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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/568,628 | 09/05/2006 | Hirohiko Hohjoh | U 016154-7 | 2748 |

140 7590 11/13/2008

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| ART UNIT | PAPER NUMBER |
| 1635 | |
| MAIL DATE | DELIVERY MODE |
| 11/13/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,628 | HOHJOH, HIROHIKO | |
| | Examiner | Art Unit | |
| | KIMBERLY CHONG | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *24,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23, 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 07/28/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 01/24/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed 07/28/2008, claims 1-28 are pending, claims 24-25 and 27-28 are withdrawn and claims 1-23 and 26 are currently under examination. Response to Applicants arguments is moot in view of the new grounds of rejection herein.

### *Information Disclosure Statement*

The information disclosure statement filed 07/28/2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the non-patent literature document listed as AR does not appear to have been filed. The IDS has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all

certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-23 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Zamore et al. (US 2005/0186586 cited on PTO Form 892 mailed 01/24/2008) as evidenced by Aravin et al. (Developmental Cell, 2003 cited on PTO Form 892 mailed 01/24/2008) and Elbashir et al. (Nature 2001 cited on PTO Form 892 mailed 01/24/2008).

The claims are drawn to a double stranded RNA (dsRNA) molecule capable of suppressing the expression of a target gene in a cell by RNAi wherein one or more nucleotides in order from the 3' end of the sense strand or one or more nucleotides in order from the 5' end of the sense strand of the double stranded part of the molecule are not complementary to the antisense strand, wherein the number of nucleotides that are not complementary are 1 to 4 or 2, wherein on additional nucleotide located at position 11-13 or position 12 from the 3' end of the sense strand is not complementary to the antisense strand, wherein one additional nucleotide located an position 1-3 in the

5' or 3' direction from a site on the sense strand of the double stranded part is not complementary to the antisense strand, wherein the dsRNA does not induce double stranded protein kinase in a cell, wherein the dsRNA has a strand length of 29 nucleotides or less and drawn to dsRNA wherein either the 5' end of the antisense or the 5' end of the sense strand are guided into the RISC.

At the outset, it must be pointed out to Applicant that the figure relied upon in Zamore et al. reference, namely Figure 6A, does in fact have support in the priority document 60/475,331 which is cited as Figure 6.

Regarding instant claims 1-3, Zamore et al. teach a dsRNA comprising a sense and antisense strand wherein up to 4 nucleotides on the sense strand are not complementary to the antisense strand (see Figure 6A, siRNA molecules miR-13b-2 and miR-124a for example). Zamore et al. refers to the antisense strand as being the guide strand that is complementary to the target sequence and is capable of being loaded into the RISC complex (see paragraph 0088). The dsRNA sequences listed in Figure 6A are duplexes wherein the sequence shown as italicized is a known miRNA sequence and as evidenced by Aravin et al., this miRNA sequence is a guide sequence, i.e. antisense strand, that is involved in guiding the RNA degradation of a target sequence (see pages 341-342 and last paragraph).

Regarding claims 4-8, Zamore et al. teach a dsRNA molecule having one or more nucleotides from the 3' position of the sense strand not complementary to the antisense strand and having a mismatch at positions 11 and 12 from the 3' end of the sense strand in the double stranded part of the molecule (see Figure 6A, specifically

mir-6-3). The dsRNA sequences listed in Figure 6A are duplexes wherein the sequence shown as italicized is a known miRNA sequence and as evidenced by Aravin et al., this miRNA sequence is a guide sequence, i.e. antisense strand, that is involved in guiding the RNA degradation of a target sequence (see pages 341-342 and last paragraph). Therefore, the italicized sequence of the dsRNA in Figure 6A is the sequence that is complementary to the target sequence and is therefore considered the antisense sequence in the dsRNA (as defined in the instant specification in paragraph 0017). It must be noted that claim 1 is not limited to just the non-complementary nucleotides being located at the 3' end of the sense strand. Claim 1 recites the dsRNA "is designed such that one or more nucleotides in order from the 3' end of the sense strand …are not complementary" and this limitation does not preclude any other nucleotide from not being complementary to the antisense strand as long as there is an adequate number of nucleotides to enable hybridization of both strands.

Regarding instant claims 9-10 and 22-23, Zamore et al. teach the dsRNA are capable of eliciting RNAi in mammalian cells and are preferably between 16-25 or 18-23 nucleotide base pairs in length which as evidenced by Elbashir et al. do not induce double-stranded RNA-dependent protein kinase. Elbashir et al. specifically teach dsRNA 30 nucleotides or less do not induce said kinase activity in cells (see pages 494-495).

Regarding instant claims 11-16, Zamore et al. teach a dsRNA wherein nucleotides starting from the 5' end of the sense strand of the double stranded part of the molecule are not complementary to the antisense strand (see Figure 6A, particularly

molecule miR-13b-2, miR-9 and miR-7, for example) and teach a dsRNA wherein one or more nucleotides starting from the 5' end of the sense strand of the double stranded part of the molecule is not complementary to the antisense strand and wherein one or more additional nucleotides, or 1 to 4, or 2 nucleotides in order from the 3' end of the sense strand of the double-stranded part are not complementary to the antisense strand.

Regarding claims 17-21, Zamore et al. teach a dsRNA wherein one nucleotide at the 5' end of the sense strand of the double stranded part of the molecule is not complementary to the antisense strand and wherein position 12 from the 3' end and/or 5' end of the sense strand is not complementary to the antisense strand (see Figure 6A, sequence miR-7 and miR-13b-2 for example). It must be noted that claim 11 is not limited to just the non-complementary nucleotides being located at the 5' end of the sense strand. Claim 11 recites the dsRNA "is designed such that one or more nucleotides in order from the 5' end of the sense strand …are not complementary" and this limitation does not preclude any other nucleotide from not being complementary to the antisense strand as long as there is an adequate number of nucleotides to enable hybridization of both strands. Therefore, the sequence miR-7 meets the limitations of the claim even though it has additional nucleotides on the sense strand that are not complementary to the antisense strand.

Regarding claim 26, Zamore et al. further teach vectors capable of expressing said dsRNA in cells (see paragraphs 0150-0153). Zamore et al. teach dsRNA with

either end comprising non-complementary nucleotides determines which sequence is guided into the RISC (see paragraph 0277).

Thus Zamore et al. anticipates claims 1-23 and 26 of the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jayasena et al. (US 20040248299), Khvorova et al. (US 2007/0031844), Elbashir et al. (EMBO Journal 2001, Vol. 20, No. 23: 6877-6888) and Holen et al. (Nucleic Acids Research 2002, Vol. 30, No. 8: 1757-1766).

Claims 1-5, 9-18, 22-23, 26 and 29-30 are drawn to the invention as stated 0000 above. Claims 6-9 and 19-21 are further drawn to a dsRNA wherein one or more mismatches from the 3' end of the sense strand of the double stranded region of the molecule are not complementary to the antisense strand and further wherein one additional nucleotide located at position 1-3 or 2 from the 3' or 5' direction from the nucleotide in the center of the sense strand is not complementary to the antisense strand wherein the site is corresponding to the cleavage site of the target gene transcription product by RISC.

Jayasena et al. teach dsRNA that are capable of mediating sequence specific gene silencing which play a significant role in understanding gene function, signal transduction pathways and identifying therapeutic agents in the future (see page 8). Jayasena et al. teach dsRNA duplexes cleaved into duplexes having strands of 21-25 nucleotides in length (see pages 1-2 and Figure 1). Jayesena et al. recognized that siRNA duplexes wherein the duplex in the middle has higher stability and the ends of each strand were more weakly associated were more capable of entering the RISC complex (see pages 21-22). Jayasena et al. do not teach the number of mismatch nucleotides on the ends of the dsRNA and do not specifically teach the mismatches in the center of the sense strand at a site that corresponds to the cleavage site of the target gene transcription product by RISC.

Khvorova et al. teach design and optimization of functional siRNA capable of sequence specific silencing gene expression wherein the siRNA comprise strands of 18-30 base pairs (see page 5). Khvorova et al. teach efficient siRNA capable of unwinding and loading into the RISC require low internal binding of the first four nucleotides on the antisense strand (see page 8 and 14).

Elbashir et al. recognized that siRNA duplexes with less base-pair strength at the 5' end of the strand of the duplex that was complementary to the target mRNA was able to act as a guide strand in mediating RNAi and was more permissive for mismatched target mRNA recognition (see Figure 1 and page 6885). Elbashir et al. further teach the position of target RNA cleavage site is located in the center of a siRNA duplex region which is 11 or 12 nucleotides downstream of the first nucleotide in the duplex region

(see page 6882). Elbashir et al. recognized that the nucleotides in the duplex region of the siRNA that were opposite the cleavage site of the target RNA are important specificity determinants and even a single nucleotide change can reduce RNAi activity. Elbashir et al. teach such siRNA are able to discriminate mutant alleles and therefore designing siRNA that have mismatches in the center of the duplex region that can discriminate between wild-type and mutant alleles can be used in therapeutic applications (see page 6885).

Holen et al. teach dsRNAs containing either one or two mismatches relative to an mRNA (see page 1763, column 1, second paragraph and Figure 6). Holen et al. teach that incorporating mismatches in dsRNAs are desirable to investigate the tolerance of the RNAi system for mismatches in the siRNA relative to the mRNA target. Figure 6 exemplifies the tolerance of RNAi for one or two mutations of the dsRNAs relative to the target mRNA.

It would have been obvious to one of ordinary skill in the art to incorporate mismatch nucleotides at the ends of the dsRNA to allow for the dsRNA to efficiently unwind and load into RISC and it would have been obvious to one of skill in the art to place mismatched nucleotide sequences in the central region of a dsRNA around the target cleavage site, as taught by Tuschl et al.

It was well known in the prior art that the strands of the siRNA are more efficiently loaded into RISC when the ends are more weakly associated as taught by Jayasena et al. and Khvorova et al. one would have wanted to incorporate mismatches and it would have been a matter of routine optimization to design siRNA comprising

various configurations of 1 to 4 mismatched nucleotide base pairs on ends to determine the optimal number that would allow efficient unwinding to mediate RNAi. Further, it was well known in the art that mismatched base pairs decrease the stability of a duplex. Moreover, given that Elbashir et al. teach a duplex with mismatched ends was able to efficiently guide the strand in mediating RNAi, one would have wanted to incorporate mismatches on the ends of the duplex. One would have expected to be able to incorporate mismatches into the ends of siRNA duplex and efficiently mediate RNAi.

Moreover, one of ordinary skill in the art would have wanted to incorporate mismatched nucleotides near the target cleavage site because such siRNA are able to discriminate mutant alleles and therefore designing siRNA that have mismatches in the center of the duplex region that can discriminate between wild-type and mutant alleles can be used in therapeutic applications. Holen et al. specifically teach that such siRNA comprising mismatches in the center of the strand exemplifies the tolerance for such mutations in RNAi and would additionally facilitate the design of dsRNA for specific targeting of mRNA that contain nucleotide polymorphisms. One would have expected to be able to incorporate mismatches at or near the cleavage site and would have been expected to be able to find the optimal position of mismatches in the central region of the duplex given both Elbashir et al. and Holen et al. teach methods of positioning the mismatches in a duplex that still allow for the siRNA to mediate gene silencing.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Examiner
Art Unit 1635